PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

REC'D 22 APR 2004
WIPO PCT

BEST AVAILABLE COPY

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed R Mahon

Dated 20 January 2004

Patents Form 1/77

THE PATENT OFFICE
31 MAR 2003
CARDIFF

Patents Act 1977
(Rule 16)

The **Patent Office**

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1.	Your reference	4-32908P1	31 MAR 2003
2.	Patent application nun *(The Patent Office will fill i*	0307440.8	01APR03 E796651-1 D00524 P01/7700 0.00-0307440.8
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number *(if you know it)*	7125487005	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic Compounds	
5.	Name of your agent *(If you have one)*		
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NJ	Novartis Pharmaceuticals UK Ltd Patents and Trademarks Wimblehurst Road HORSHAM West Sussex RH12 5AB ADP No 0718522002
	Patents ADP number *(if you know it)*	1800001	
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country / Priority nu *(if you*	
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	Yes	
	a) any applicant named in part 3 is not an inventor, or		
	b) there is an inventor who is not named as an applicant, or		
	c) any named applicant is a corporate body.		
	(see note (d))		

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	10
Claim(s)	1 DL
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co. Date **31st March 2003**

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom **Mrs. S. Schnerr**
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

Organic Compounds

This invention relates to an oral suspension of tegaserod or pharmaceutically acceptable salts thereof. In particular, it relates to an oral suspension comprising a powder comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof in a beverage.

Tegaserod (3-(5-methoxy-1H-indol-3-yl-methylene)-N-pentylcarbazimidamide) and pharmaceutically acceptable salts thereof (also "the Active Agents of the invention"), e.g. hydrogen maleate or hydrochloride, and their manufacture are known e.g. from EP 505322 (herein incorporated by reference) and under the trademarks ZELMAC® and ZELNORM®. The Active Agents of the invention are serotonergic active agents acting on the gastro-intestinal system as partial agonists of the 5-HT_4 receptor and are useful for the prevention and treatment of gastrointestinal motility disorders, e.g. Irritable Bowel Syndrome (IBS), Gastro-Esophageal Reflux Disease (GERD), Functional Dyspepsia (FD), Post Operative Ileus (POI), Diabetic gastroporesis and chronic constipation. Published PCT Application WO 00/10526 describes solid oral pharmaceutical compositions of e.g. tegaserod with its use in gastrointestinal motility disorders including the solid tablet formulation of tegaserod which is at time of filing this application the currently being marketed tablet form in several countries, e.g. the U.S. and Australia (herein after referred to as "the marketed tablet of tegaserod" or "the currently marketed tablet of tegaserod").

Despite the merits of the above-mentioned compositions, there remains the problem for patient who have difficulties to take their tegaserod formulation, e.g. have difficulties to swallow the solid dosage form. For example, elderly or senile patients, mentally handicapped patients, severely injured patients, patients after surgery, e.g. suffering from POI may require special administration of the tegaserod drug, e.g. in the form of beverage. Thus there is a marketing need to have a liquid formulation for tegaserod with acceptable criteria of dissolution, stability and homogeneity. At the moment, tegaserod is not commercially available as a liquid formulation at all but only as a solid tablet. Furthermore, tegaserod is only commercially available as a 6 mg and in a few countries as a 2 mg tablet. Both tablet formulations do not have a partition line. Thus there is no straight forward possibility for a doctor to administer tegaserod in a particular dosage other than 6 or 2 mg. As the herein disclosed oral suspensions of tegaserod are homogenous, the invention allows partitioning

of the dose with ease. Moreover, the mixture of crushed tablets of tegaserod with particular aqueous solutions has a sufficient stability profile.

The present invention relates in a first aspect to an oral suspension comprising a mixture in divided form comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof, and a beverage.

More preferably the present invention relates in a first aspect to an oral suspension comprising a mixture in a divided form comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof, and a beverage; said suspension having a dissolution characteristic for tegaserod in water of more than about 80% after 30 minutes, preferably more than about 90% after 30 minutes, more preferably more than about 80% after 5 minutes, and more preferably more than about 90% after 5 minutes.

The oral suspension has preferably a pH above about 2, more preferably above about 3. The beverage may be added to the powder at a ratio of e.g. 6 mg tegaserod and e.g. about 10 to about 100 ml, more preferably to about 50 ml.

The preferred pharmaceutically acceptable salt of tegaserod is the hydrogen maleate salt.

For the purpose of this invention, the beverage is defined as any liquid that is fit for drinking (The Roget's II: The New Thesaurus, Third Edition, 1995). It may be a drink of any type that can be purchased e.g. in a supermarket or obtained from the tap. The beverage can be e.g. milk, water, apple juice or orange juice.

For the purpose of this invention, a "mixture in divided form" may be a powder, a granulate, a grind, a pulver or particles.

In a preferred embodiment, the present invention relates to an oral suspension as described above; whereas said mixture in a divided form is a crushed tablet. The crushed tablet may be obtained by crushing a tablet of tegaserod, preferably the currently marketed tablet of tegaserod, more preferably one tablet of the currently marketed tablet of tegaserod, e.g. as described below. The crushed tablet should be understood as a part or parts of a tablet or one or more tablets, preferably one tablet.

In a further preferred embodiment, the present invention relates to an oral suspension as described above; whereas the beverage has a task-masking effect, able to overcome the bitter taste of tegaserod, e.g. is apple juice.

In a further aspect the present invention relates to a process to make the mixture in divided form, e.g. powder as described above comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof. The process comprises the steps of packing a tablet comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof in a piece of aluminum foil and crushing said tablet into a mixture in divided form, e.g. powder.

A preferred preparation of the oral suspensions comprises the following steps:

- take out one 6 mg marketed tablet of tegaserod from the blister
- cut a piece of aluminum foil (food quality) of approx 10 x 10 cm
- place the Tablet on the center of the aluminum foil piece
- bend double the aluminum foil piece and fold back the 3 open sides in order to get a closed pouch with the tablet inside
- place the aluminum pouch on a flat and hard surface (e.g. on a table)
- take a tea-spoon and crush the tablet firmly with the back of the spoon through the aluminum foil until the tablet breaks into a mixture in divided form
- open carefully the aluminum pouch , in order to avoid any loss of mixture in divided form, and pour the mixture in divided form into the beverage, e.g. 50 ml apple juice
- carefully mix with a tea spoon (or a spatula) during one minute.

In a further aspect, the present invention relates to an oral suspension as described above, whereas said mixture having the dissolution characteristics in water of

Time (minutes)	% of theoretical content dissolved (mean)
5	> 80
15	> 85
30	> 90.

The oral suspension of the present invention are useful in the known indications of the particular active agent incorporated therein. For example, said oral suspensions are useful in

the prevention and treatment of gastro-intestinal disorders and anal continence dysfunctions, e.g. in Irritable Bowel Syndrome (IBS), Functional Dyspepsia (FD) and gastroesophageal reflux disease (GERD).

Tegaserod is known. Its manufacture and therapeutic use in the prevention and treatment of gastro-intestinal disorders and anal continence dysfunctions are described in e.g. EP 505322 which is incorporated herein by reference. Commercially available dosage forms are provided for oral administration, for example tablets comprising 2 and 6 mg of active ingredient. Those dosage forms are known by the trademark ®Zelmac or ®Zelnorm (Novartis) and have been introduced in a large number of countries, such as the U.S., Australia, South Korea and Switzerland.

The exact amounts of active agent, tegaserod, and of the oral suspension to be administered depend on a number of factors, e.g. the condition to be treated, the desired duration of treatment and the rate of release of active agent.

For example, the amount of tegaserod required and the release rate thereof may determined on the basis of conventional in vitro and in vivo techniques, determining how long the tegaserod blood plasma level remains at an acceptable level for a therapeutic effect. Examples of doses provided in a solid formulation to human patient (= effective amount of tegaserod), e.g. a tablet, are 0.5 to 12 mg BID (= twice a day) of tegaserod, for IBS and 0.5 to 12 mg BID and 0.5 to 6 mg TID (= three times a day) of tegaserod for FD and 0.2 to 12 mg BID of tegaserod for GERD, irrespective of the body weight.

The following examples illustrate the invention.

Examples

The following beverages and tablets are used for the Examples:

- Water (drinking water from tap)
- Apple juice (Auchan)
- Orange juice (Tropicana, pure premium)
- Milk (skimmed milk, Auchan)
- Composition of a 6 mg tegaserod tablet (according to Example 3 and 4 of WO 01/0526):

• Tegaserod maleate	8.31 mg (6mg base)
• Polyplasdone XL USP/NF	50.00 mg
• Glyceryl monostereate USP/NF	12.50
• Poloxalkol	2.50
• Lactose 200 mesh	37.94
• HPMC 3cPs	6.25
• Polyethyleneglycol 4000	7.50
• Water adsorbed	3.00
• Total	128 mg

- Composition of a 2 mg tegaserod tablet (according to Example 1 and 2 of WO 01/0526):

• Tegaserod maleate	2.77 mg (2mg base)
• Polyplasdone XL USP/NF	36.00 mg
• Glyceryl monostereate USP/NF	9.00
• Poloxalkol	1.80
• Lactose 200 mesh	30.53
• HPMC 3cPs	4.50
• Polyethyleneglycol 4000	5.40
• Water adsorbed	2.00
• Total	92 mg

Example 1: Stability Study of the oral suspensions of the present invention

The stability study is performed for maximum 3 days at the storage conditions of room temperature (about 20-25 °C) and/or 5°C (fridge) . The start point (T0) is performed about 1 minute after preparation. Furthermore, a "24 hours" and "3 days" time point at room temperature and 5°C is performed.

Analytical methods: For each time-point tested, the degradation products of Tegaserod by HPLC are evaluated. Analytical methods are based on Test Methods described below.

Procedure for assay determination: For each time-point, one tablet is crushed according to the above procedure. The crushed tablet is transferred quantitatively into a 100 ml amber glass volumetric flask. 50 ml of the beverage is carefully added and the suspension is shaken vigorously by hand a few time and allowed to stand for the storage time tested. The suspension is re-homogenized, by shaking by hand. For extraction, the flask is filled to the mark with methanol (about 50 ml) then shaken for 30 minutes under magnetic stirring, sonicated for 10 minutes and shaken for 30 minutes under magnetic stirring. An aliquot of the methanol solution is centrifuged. The clear supernatant of the above solution is used as the test solution and is analyzed by HPLC (Isocratic HPLC on reversed phase RP-8 with UV detection). The same procedure is carried out once for each beverage but without tablet powder and the resulting chromatograms are compared for new appearance of any peak.

Procedure for determination of degradation products: In order to enable to reach a sufficiently low limit to quantify the degradation products, the number of tablets to be crushed is increased. For each time-point, 6 tablets for 2 mg dosage strength (or 5 tablets for 6 mg dosage strength) are crushed according to the above procedure. The crushed tablet is transferred quantitatively into a 20 ml for 2 mg dosage strength (or 50 ml amber glass volumetric flask for 6 mg dosage strength). 10 ml for 2 mg dosage strength (or 25 ml for 6 mg dosage strength) of the beverage are added carefully. The suspension is shaken vigorously by hand a few time and is allowed to stand for the storage time tested. The suspension is re-homogenized by shaking by hand. For extraction, the flask is filled to the mark with acetonitrile and is shaken for 30 minutes under magnetic stirring, sonicated for 10 minutes and shaken for 30 minutes under magnetic stirring. An aliquot of the homogenized solution is centrifuged.

The clear supernatant of the above solution is used as the test solution in order to quantify using a gradient HPLC on reversed phase RP-8 with UV detection. The same procedure is carried out once for each beverage but without crushed tablet and the resulting chromatograms are compared and analyzed according to the scheme below.

Acceptance criteria: Tegaserod is assumed stable in the tested media if the following acceptance criteria are met for the time-points studied.

Table of Acceptance Criteria		**Values of acceptance**
Assay	start after storage	90.0 - 110.0 % Not more than 3 % less than the start value*
Degradation		
product 5-methoxy-1H-indole-3-carbaldehyde	For all time-points	≤ 0.5 %
Degradation products which are not known	For all time-points	Each individual ≤ 0.2%** All together: ≤ 1.0 %**

Tegaserod is stable in apple juice, orange juice and water for at least 1 hour at room temperature and for up to 3 days in the fridge (for 6 mg dosage strength) or for at least 24 hours in the fridge (for 2 mg dosage strength).

Example 2: Completeness of administration and homogeneity of the content

The following beverages are used for the study:

- Tap water (drinking water from tap)

---

* 2 % (usual difference allowed between 2 analysis of the same sample generated in 2 different laboratories) + 1 % (sum of degradation product allowed)

** Current specifications (stability) for Degradations Products for Zelmac tablets

- Apple juice (Auchan)
- Orange juice (Tropicana, pure premium)
- Milk (half skimmed, Auchan)

When taking the medication with a beverage, the procedure followed by the patient comprises crushing of the tablets, mixing the crushed tablet with the beverage in a glass, and drinking the content of the glass. It is important to verify whether under those conditions, the complete dose is taken by the patient. Consequently the test described below as "completeness of administration" is performed *(this is described by the assay method below).* In addition, the homogeneity of the content of tegaserod in all solutions is tested in order to determine if the mixture could be apportioned to administer lower doses.

Analytical procedure: The test is performed using HPLC as above (reversed phase RP-8 with UV detection):
The crushed tablet resulting from the crushing of one tablet is transferred quantitatively into a glass containing about 50 ml of the tested beverage. The suspension is stirred using a tea spoon.
- For completeness of administration: the content of the glass is transferred quantitatively to a 100 ml amber glass volumetric flask (this simulate the drinking of the beverage by the patient: the glass was NOT rinsed) which is immediately filled with to the 100 ml mark methanol.
- For homogeneity of content: 15 ml of the solution in the glass (exactly 30 % of the totality of the solution) is withdrawn and transferred quantitatively to a 100 ml amber glass volumetric flask and immediately fill to the 100ml mark with methanol.
For extraction, the flask is filled to the mark with acetonitrile and is shaken for 30 minutes under magnetic stirring, sonicated for 10 minutes and shaken for 30 minutes under magnetic stirring. An aliquot of the homogenized solution is centrifuged.

The clear supernatant of the above solution is used as the test solution in order to quantify using a gradient HPLC on reversed phase RP-8 with UV detection. The same procedure is carried out once for each beverage but without crushed tablet and the resulting chromatograms are compared and analyzed according to the scheme below.

Acceptance criteria

Table of Acceptance Criteria		Values of acceptance
Assay	Whole amount of the patient sample analyzed	90.0 - 110.0 % of theoretical content
	Fraction of the patient sample analyzed	For information only.

The homogeneity of the mixtures with apple juice, water and orange juice is judged adequate and would allow fractionating of the dose. No loss of drug product during administration according to the recommended procedure for the suspensions with apple juice, water and orange juice is observed. Suspensions with milk are considered inhomogeneous as only about 70% of the dose would be taken by the patient (due to probably adsorption to the glass). In addition, the drug substance is not homogeneously distributed in the oral suspension.

Example 3: In vitro dissolution tests

The following beverages and food are used for the study:

Tap water (drinking water from tap)

Apple juice (Auchan)

Orange juice (Tropicana, pure premium)

In vitro dissolution tests are performed according to the following conditions : dissolution medium = water (500 ml), USP apparatus 2 at 50 rpm (apparatus described in the United States Pharmacopeia, type 2 = rotating paddle apparatus; 50 rpm rotating speed of the paddle). All tests are performed on 6 units. Quantitative determination of dissolved tegaserod in medium is done with Isocratic HPLC on reversed phase RP-8 with UV detection.

The test is done with :

- the crushed tablets dispersed in 50 ml water
- crushed tablets dispersed in 50 ml of orange juice
- crushed tablets dispersed in 50 ml of apple juice

- Tablets:

For comparison, the dissolution profiles of the same tablets batch are used.

- Crushed tablets in water:

Dissolution is performed for 3 units by addition of the crushed tablet into the 500 ml of dissolution medium. Since wettability problem is expected with the crushed tablet, for the 3 other units, the crushed tablet is put at the bottom of the dissolution vessel prior to addition of the dissolution medium. No significant difference is observed for results of both operational procedure, consequently averaged results on 6 units are reported.

- Crushed tablets in juices:

The powder resulting from the crush tablet according to the procedure above is added to 50 ml of juice in a glass and homogenized using a spatula. The mixture is added to 450 ml of dissolution medium without rinsing the glass. As a result, the volume of the dissolution medium is 500 ml. No significant difference is observed between the dissolution profile of the crushed tablets and of the tablets. The only difference observed is the higher amount already dissolved at 5 min for the crushed tablet which is due to the fact that no disintegration of the tablet is needed prior to dissolution. After 15 min dissolution profiles are comparable and a complete dissolution is observed for all 6 units, i.e. more than 85 % dissolved. Dissolution profile of crushed tablets are thus the same as in the specifications for Zelmac tablets. The same conclusion applies to the apple juice. No significant difference is observed between the dissolution profile of the crushed tablets mixed with apple juice and the one of the tablets in water. The dissolution profile of the orange juice is less favorable, i.e. around 58% after 60 minutes.

Example 4: Masking of the bitter taste of tegaserod

The palatability of the resulting suspensions is determined by the subjective impression of one test person. Thus, it is found by this evaluation that the bitter taste of tegaserod is masked in apple juice and in orange juice but not in water.

Claims

1.) An oral suspension comprising a mixture in divided form comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof and a beverage.

2.) The oral suspension of claim 1; having a dissolution characteristic in water of more than about 80% after 30 minutes.

3.) The oral suspension of claim 1; whereas the dissolution characteristic in water is more than about 90% after 30 minutes.

4.) The oral suspension of claim 1; whereas the dissolution characteristic in water is more than about 80% after 5 minutes.

5.) The oral suspension of any of the preceding claims; whereas said mixture in divided form is a crushed tablet comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof.

6.) The oral suspension of any of the preceding claims; whereas the crushed tablet is one crushed tablet comprising an effective amount of tegaserod.

7.) The oral suspension of claims 1 to 5; whereas a crushed tablet is one crushed tablet comprising an effective amount of tegaserod maleate.

8.) The oral suspension of claims 1 to 5; whereas a crushed tablet is one crushed tablet comprising 6 mg tegaserod.

9.) The oral suspension of claims 1 to 5; whereas a crushed tablet is one crushed tablet comprising 2 mg tegaserod.

10.) The oral suspension of any of the preceding claims; whereas the beverage is able to mask the bitter taste of tegaserod.

11.) The oral suspension of any of the preceding claims; whereas the beverage is apple juice.

12.) The oral suspension of any of the preceding claims; whereas the beverage is water.

13.) The oral suspension of any of the preceding claims; comprising 10 to 100 ml of the beverage.

14.) The oral suspension of claim 13; whereas the beverage is apple juice.

15.) A process to prepare an oral suspension of any preceding claims, comprising packing a tablet comprising an effective amount of tegaserod or a pharmaceutically acceptable salt thereof in a piece of aluminum foil and crushing said tablet into a mixture in divided form.